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Omphalocele in Miller-Dieker Syndrome: Expanding the Phenotype

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We report on a patient prenatally diagnosed with omphalocele, mild cerebral ventriculomegaly, nuchal fold thickening, and cystic changes in the umbilical cord who was found postnatally to have lissencephaly type I. Prenatal chromosome analysis showed a normal male karyotype; however, postnatal high resolution banding and FISH analysis, using a probe for locus D17S379 in chromosome region 17p13.3, demonstrated a deletion at 17p13.3 consistent with Miller-Dieker syndrome (MDS). A review documented four more cases with MDS/isolated lissencephaly/17p-, with omphalocele. Because MDS is a contiguous gene disorder, we speculate that a gene or genes in this region have a major role in the closure of the lateral folds or the return of the midgut from the body stalk to the abdomen at 5–11 weeks of gestation. Prenatal diagnosis of omphalocele with mild ventriculomegaly should prompt FISH analysis for a deletion in 17p13.3. Am. J. Med. Genet. 69:293–298, 1997.

KEY WORDS: lissencephaly; fetal ultrasound (U/S); omphalocele; cerebral ventriculomegaly; thick nuchal fold; Miller-Dieker syndrome; del (17)(p13.3); chromosome abnormality; FISH analysis

INTRODUCTION

Miller-Dieker syndrome (MDS) is a contiguous gene disorder characterized by lissencephaly type I (agyria with thick cortex and normal cerebellum), and characteristic facial anomalies, severe developmental delay, and seizures [Dobyns et al., 1991]. In some cases, noncraniofacial abnormalities, such as congenital heart disease, clinodactyly, camptodactyly, cryptorchidism and sacral dimple among others, may be present [Dobyns et al., 1984]. The facial anomalies include a high, prominent and wrinkled forehead, bitemporal hollowing, short and pointed nose with anteverted nostrils, long upper lip with thin upper vermilion border, and micrognathia. More than 90% of the patients with MDS have a microdeletion at 17p13.3, which can be detected by high resolution banding and more recently by FISH analysis [Kuwano et al., 1991; Ledbetter et al., 1992].

Prenatal diagnosis of Miller-Dieker syndrome during the second trimester of pregnancy, in cases not at risk, is not feasible because the fetal ultrasound findings, including mild ventriculomegaly, polyhydramnios, IUGR, and in some cases, noncraniofacial abnormalities such as cardiac abnormalities [Dobyns et al., 1984], are nonspecific and the routine fetal chromosome analysis will not detect small deletions in 17p13.3.

We report on a patient who presented prenatally with mild cerebral ventriculomegaly and omphalocele and who was found postnatally to have Miller-Dieker syndrome. A review demonstrated two other cases of MDS with an omphalocele [Alvarado et al., 1993]: one case with lissencephaly type I [Dobyns et al., 1992] and another case with 17p- [Sermer et al., 1987]. We propose that in these cases, the deleted segment in 17p13.3 includes a gene or genes involved in the normal development of the ventral body wall. We recommend that fetuses detected prenatally to have omphalocele and mild ventriculomegaly be tested specifically for Miller-Dieker syndrome by FISH analysis and, if possible, with a fetal brain MRI [Okamura et al., 1993].

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CLINICAL REPORT

A 26-year-old G2P1 mother was referred after a fetal ultrasound (US) study showed omphalocele and borderline cerebral ventriculomegaly. The mother was of English-Italian descent and her husband was of the same age and of French-Canadian descent. The couple were nonconsanguineous and healthy. They have a 3-year-old son with mild developmental delay who had seizures at age 2 years. The couple's family histories were noncontributory.

The pregnancy was uncomplicated during the first 16 weeks and a fetal US study done at 14 weeks of gestation was interpreted as normal. A repeat fetal US study at 16 weeks of gestation showed omphalocele, and a detailed fetal US study at 20 weeks of gestation confirmed the presence of an omphalocele containing liver with borderline ventriculomegaly, 9–10 mm (Fig. 1) and thick nuchal fold, 6.2 mm. Fetal echocardiography showed a normal cardiac anatomy, and maternal STORCH analysis was negative. The parents decided to have amniocentesis, which was done at 20 weeks of gestation. FISH analysis using probes for chromosomes X,Y,13,18, and 21 (Oncor, Gaithersburg, MD) demonstrated a male karyotype and ruled out aneuploidy for these chromosomes. Subsequent fetal chromosome analysis showed a normal male karyotype: 46,XY. The amniotic fluid-AFP was 1.02 MoMs, and the amniotic fluid viral culture was negative. The couple elected to carry the pregnancy to term and a repeat fetal US study at 24 weeks' gestation demonstrated cysts along the umbilical cord (Fig. 2), a small omphalocele that contained mainly liver, mild dilatation of the lateral cerebral ventricles (10 mm) (Fig. 3), and normal fetal growth. Retrospective review of the fetal US study done at 36.6 weeks of gestation showed an immature insular opening and a smooth brain surface [Fig 4]. Fetal assessments at 35, 36, and 37 weeks gestation were normal.

Fig. 1. Transverse view through fetal head at 19 weeks of gestation showing the occipital horn of the lateral ventricle (V) to measure 9.6 mm, which is at the upper normal range.

Fig. 2. Transverse view of fetal abdomen at 24 weeks of gestation shows small omphalocele containing a segment of liver (L) cyst along the umbilical cord.

Delivery induced at 37 weeks gestation was vaginal and uncomplicated. The Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Birthweight was 2.75 kg (30th centile), length 47 cm (30th centile), and OFC 34.5 cm (40th centile). The facial appearance was consistent with Miller-Dieker syndrome (Fig. 5). The anterior fontanelle measured 3 × 3 cm, the posterior 0.2 × 0.2 cm, and a third fontanelle 0.2 × 0.2 cm. The scalp hair was blond, the forehead was high with bitemporal hollowing, frontal bossing, and wrinkling when he cried. There were hypoplastic supraorbital ridges, hypertelorism [IC-mean; OC-+2SD; IP-+2SD; PF-mean],

Fig. 3. Transverse view through fetal head at 24 weeks of gestation showing the prominent occipital horn, which measures 10 mm. Although this measurement is normal, the distance between the medial wall of the ventricle and choroid (arrow) is widened to 5 mm, which is larger than normal. The appearance of the insula (open arrow) is normal for this gestational age as is the absence of sulci at the cortical surface.

Fig. 4. Transverse view through the fetal head at 36.6 weeks of gestation taken incidentally at time of fetal biophysical assessment. Detail is poor, but the insula (arrow) has an immature open appearance without the usual overfolding of the temporal lobe. Also, no sulci are visible at the surface of the brain (open arrow) and they usually can be seen by this age. These findings are in keeping with lissencephaly.

bilateral epicanthic folds and bilateral infraorbital creases. The nasal bridge was depressed, and the nose was small and pointed with anteverted nostrils. The upper lip was long (+2SD) with a narrow upper vermilion border. The palate was intact, and there was micrognathia with a pointed chin. The ears were well formed. The occiput was flat and there was a redundant nuchal skin. Chest and cardiac findings were normal and examination of the abdomen showed a three-vessel cord with an omphalocele measuring 5 cm in diameter, covered with a membrane that contained part of the liver. The genitalia were normal and both the upper and lower limbs were held in a "froglike" position.

The omphalocele was repaired shortly after delivery without any post-operative complications. A head US study demonstrated absence of cerebral sulcation consistent with diffuse lissencephaly. The cerebral ventricles appeared normal and partial agenesis of the corpus callosum was suggested. The grey/white matter differentiation was diffusely abnormal. Brain MRI showed no gyral formation and very "primitive" Sylvian fissures consistent with lissencephaly type I (Fig.

Fig. 5. The patient at 2 weeks showing the characteristic facial traits of Miller-Dieker syndrome, including high forehead, frontal bossing with bitemporal narrowing, small nose with anteverted nostrils, prominent upper lip, and micrognathia.

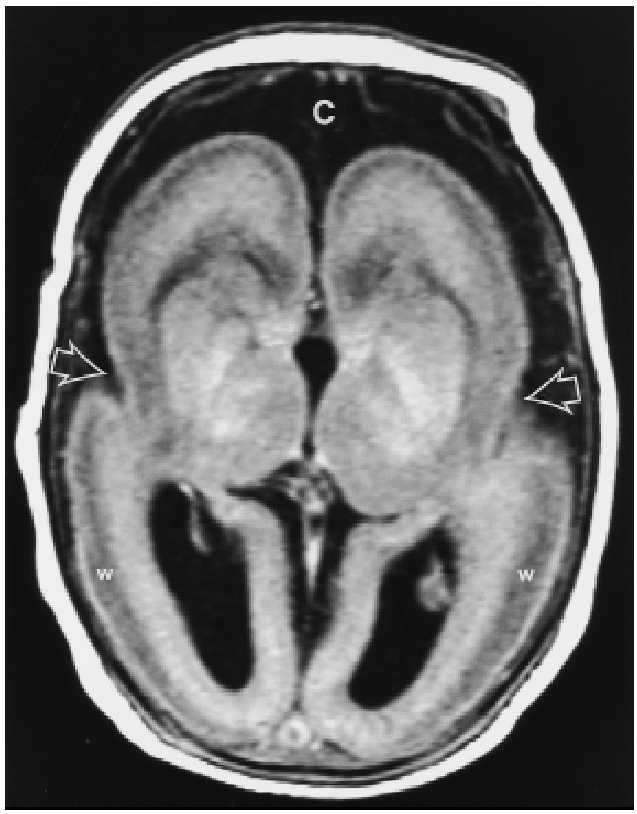

Fig. 6. MRI of the newborn infant (axial T1 weighted TR500/TE20) shows diffuse and complete type I lissencephaly. There is a thin outer cortical layer separated from a thicker, inner cortical layer by a layer of white matter (W). On this MRI, the white matter (W) appears slightly grey in contrast to the cortex, which has a lighter shade. Primitive Sylvian fissure (open arrows) are visible bilaterally and give rise to a "figure 8" appearance of the brain. The posterior horns of the ventricular system have a persistent fetal configuration also called colpocephaly. Prominent CSF spaces (C) are seen over the convexities. Hypogenesis of the corpus callosum and a normal cerebellum (not shown) were also confirmed on MRI.

6). The CSF spaces and ventricles were diffusely enlarged with hypogenesis of the corpus callosum and normal cerebellum. FISH analysis using a probe for D17S379 (Oncor, Gaithersburg, MD) showed a deletion in 17p13.3 (Fig. 7). The patient's parents and brother had normal chromosomes by G-banding and FISH analysis.

At age 4 weeks, the patient started to convulse with tonic extension of arms and legs, loss of consciousness, and circumoral cyanosis. The seizures lasted 5–10 sec and repeated itself every 20 min; there was poor response to anticonvulsive medications. No feeding difficulties were noted when he was conscious. At 4 months, his weight and length were below the 3rd centile and the OFC was at the 3rd centile. His facial structure remained unchanged. He was in opisthotonic position, did not follow or smile, had a truncal hypotonia, and increased tone in all four limbs. His deep tendon reflexes were +1 in the upper limbs and +2 in the lower limbs. The rest of his physical findings were unremarkable.

DISCUSSION

Lissencephaly is a rare neurodevelopmental disorder, resulting from a defect in neuronal migration at 10–14 weeks of gestation. The incidence of lissencephaly was estimated to be 1:13,000–1:20,000 [Dobyns et al., 1993] live births and the postnatal diagnosis is based on head US study, brain MRI, and CT scan findings. Based on the histopathological and neuroradiological findings, Dobyns et al. [1984] recognized two types of lissencephaly: type I with thick cortex, and neither hydrocephalus nor cerebellar abnormalities, and type II with obstructive hydrocephalus and cerebellar malformation. In both types, the cerebral cortex contains four instead of six layers because of the arrest in neuronal migration [Dobyns et al., 1993]. Although the first reported cases of lissencephaly were with complete agyria, further studies showed that agyria is the most severe neuropathological manifestation of this disorder with pachygyria at the mild end of the spectrum. The neuroradiological, neuropathological findings define four grades of lissencephaly: grade 1 with complete agyria; grade 2 with widespread agyria and a few sulci restricted primarily to the frontal and temporal poles and basal frontal lobe; grade 3 with extensive areas of both agyria and pachygyria and grade 4 with a widespread pachygyria without areas of agyria [de Rijk-van Andel et al., 1990; Dobyns et al., 1992].

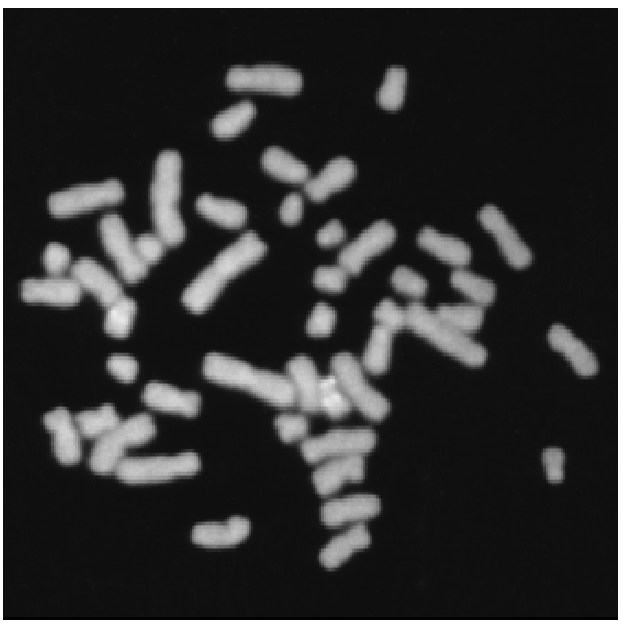

Fig. 7. Digoxigenin-labelled probe (Oncor) for locus D17S379 in 17p13.3 was hybridized to metaphase chromosomes along with the RARA probe in 17q21 as an internal control. Antidigoxigenin-FITC was used to visualize the hybridization. Chromosomes were counterstained with propidium iodide. One chromosome 17 lacked a signal at 17p13 indicating the presence of a deletion.

Lissencephaly is a heterogeneous disorder and can result from non-genetic causes such as intrauterine infection with cytomegalovirus or rubella and poor perfusion or have a genetic basis, which include microscopic and submicroscopic chromosome abnormalities as well as single gene disorders [Pilz et al., 1996]. The most common genetic cause of lissencephaly type II is the Walker-Warburg syndrome. This is an autosomal recessive disorder comprising agyria, retinal dystrophy, hydrocephalus, muscular dystrophy, cerebellar abnormalities, and in some cases encephalocele [Chitayat et al., 1995].

The classification of genetic conditions with lissencephaly type I underwent major changes due to improvements in cytogenetic techniques, DNA analysis and the introduction of FISH analysis, which enabled identification of submicroscopic deletions and duplications. In 1963, Miller reported a family with two children with type I lissencephaly and in 1969, Dieker et al. reported a second family with multiple children with the same type of lissencephaly. Based on these reports, the condition was concluded to be a single gene disorder with an autosomal recessive mode of inheritance, which Jones et al. [1980] named Miller-Dieker syndrome. The condition consists of lissencephaly, a prominent forehead, bitemporal hollowing, short nose with upturned tip and anteverted nostrils, long and protuberant upper lip with a thin upper vermilion border, and a small jaw [Dobyns et al., 1992]. Patients with lissencephaly but without the characteristic facial anomalies were categorized by Dobyns et al. [1992] as having isolated lissencephaly (ILS).

In 1983, Dobyns et al. reported the first cases of MDS associated with del(17)(p13), and chromosome analysis done on the familial cases reported by Miller [1963] showed that the father had a chromosome rearrangement [46,XY,t(15;17)(q26.1;p13.3)] and the affected members were carriers of an unbalanced rearrangement. Furthermore, the same studies done on the family reported by Dieker et al. [1969] detected a chromosome rearrangement, [46,XY,t(12;17)(q24.31;p13.3)], with the affected members of the family being carriers of an unbalanced rearrangement [Stratton et al., 1984]. The conclusion was that Miller-Dieker syndrome is a contiguous gene disorder caused by haplo-insufficiency of a gene or genes having a major role in the development of the brain and face. Further investigation of

familial and sporadic cases using initially high resolution chromosome banding and later Southern blot analysis of restriction fragment length polymorphism with several different DNA markers in 17p13.3 and later FISH analysis using different DNA probes of this segment documented that at least 90% of patients with Miller-Dieker syndrome and 38% of the cases with isolated lissencephaly have a microdeletion in a critical 350 kb region of chromosome 17p13.3 [Dobyns et al., 1993]. Recently, a gene (LIS-1), deleted in MDS was identified and the deduced amino-acid sequence showed significant homology to beta subunits of heterotrimeric G proteins, suggesting that the gene may have a major role in brain development [Reiner et al., 1993]. Furthermore, Hattori et al. [1994] reported the homology of bovine platelet activating factor acetylhydrolase (PAFAH) to LIS-1 gene, suggesting that a partial or complete deletion of a gene encoding a 45 Kd subunit of PAFAH was the cause of MDS. However, Chong et al. [1995] found that the minimal critical region of ILS was distal to PAFAH-45K, and therefore other candidate gene/genes involved in the cause of lissencephaly in ILS/MDS remain unidentified.

Apart from the characteristic facial and brain abnormalities, MDS includes other defects including polydactyly, small external genitalia and cryptorchidism, sacral dimple, and congenital heart disease, among others. Sermer et al. [1987] reported on a newborn infant with omphalocele and congenital heart disease and 17p- karyotype. The baby died at 10 months, and no further information regarding the deletion and the brain abnormality was given. Dobyns et al. [1992] reported a sporadic case with lissencephaly and omphalocele. Detailed cytogenetic or FISH analysis were not provided. In 1993, Alvarado et al. reported two sibs with deletion 17p13.3, which resulted from a paternal cryptic translocation [46,XY,t(17;19)(p13.3;q13.33)]. Both children were born with lissencephaly type I, characteristic facial changes of Miller-Dieker syndrome and omphalocele. The deletion in the children was identified by FISH analysis. Thus the case reported by us is the fifth reported case of Miller-Dieker syndrome/17p-/isolated lissencephaly associated with omphalocele.

Prenatal diagnosis of lissencephaly type II was reported and may be easy to detect since the cerebellar hypoplasia, hydrocephalus, and in some of the cases, the encephalocele, can be detected prior to 24 weeks of gestation [Chitayat et al., 1995]. However, in lissencephaly type I, the findings on fetal ultrasound are not always diagnostic or easy to identify. Fetal ultrasound abnormalities found in cases with lissencephaly include nonspecific changes such as cerebral ventriculomegaly, hypoplasia/agenesis of the corpus callosum, microcephaly, and polyhydramnios. A large Sylvian fissure, characteristic of lissencephaly type I, is difficult to diagnose prenatally [Salzman et al., 1991]. In our patient, the ventriculomegaly was mild, and neither microcephaly nor polyhydramnios were detected. Moreover, despite frequent detailed fetal ultrasounds, the agenesis of the corpus callosum, which was detected on postnatal MRI, could not be identified.

Omphalocele is a ventral wall defect with herniated intra-abdominal organs, located at the base of the umbilical cord and covered by amnioperitoneal membrane. The incidence of nongastrointestinal abnormalities is high with cardiac [Crawford et al., 1985], genitourinary [Rott and Truckenbrodt, 1974], and neural tube defects [Czeizel, 1981] detected in ~40% of the cases. Most cases are sporadic and in a small number of cases, the omphalocele can be the result of a single gene disorder [Table I]. Microscopic chromosome abnormalities were found in 10% of the liveborn babies with omphalocele and in ~ 30% of fetuses detected in the second trimester [Baird and MacDonald, 1981; Sermer at al., 1987; Van de Geijn, 1991]. However, prenatal karyotyping, as done in our case, cannot detect submicroscopic chromosome deletions or duplications. As illustrated with our case, this can result in false reassurance of the parents unless a specific diagnosis such as MDS is suspected and appropriate FISH analysis is carried out.

TABLE I. Single Gene Disorders Associated With Omphalocele

Disorder	OMIM#	References
Autosomal recessive		
Omphalocele-cleft palate	258320	Czeizel [1983]
OEIS complex	258040	Smith et al. [1992]
Opitz C syndrome	211750	Cabral de Almeida et al. [1992]
Craniosynostosis-mental retardation syndrome of Lin and Gettig	218649	Lin et al. [1990]
Agonadism with multiple internal malformation	202660	Kennerknecht et al. [1993]
Hydrocephalus with associated malformation	236640	Game et al. [1989]
Hydrolethalus syndrome	236680	Pryde et al. [1993]
Malpuech facial clefting syndrome	248340	Guion-Almeida [1995]
Agonadism, XY, with mental retardation, short stature, retarded bone age, and multiple extragenital malformations	600908	Kennerknecht [1995]
Diaphragmatic defects, limb deficiencies and ossification defects of skull	601163	Froster et al. [1996]
Autosomal dominant		
Shprintzen syndrome	182210	Shprintzen et al. [1979]
Omphalocele	164750	DiLiberti [1982]
Beckwith-Wiedemann syndrome	130650	Beckwith [1969]
X-linked		
Omphalocele	310980	Havalad et al. [1979]
Melnick-needles osteodysplasty	309350	von Oeyen et al. [1982]
Cranioorodigital syndrome	304120	Young et al. [1993]
Thoracoabdominal syndrome	313850	Carmi et al. [1990]
Simpson-Golabi Behmel syndrome	312870	Weksberg [1996]

The association of MDS with omphalocele suggests that the chromosome segment 17p13.3 contains a gene or genes having a major role in the closure of the lateral folds or the return of the midgut from the body stalk to the abdomen at 5–11 weeks of gestation. Thus sporadic conditions such as pentalogy of Cantrel and autosomal dominant conditions such as familial omphalocele [OMIM # 164750] may be the result of a deletion or mutation in a gene located in 17p13.3. Therefore, we suggest that the detection of omphalocele with brain abnormality (including mild ventriculomegaly) should prompt not only routine fetal karyotyping, but also FISH analysis looking for deletion in 17p13.3.

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